

Ses i 1-specific IgE and sesame oral food challenge results

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Clinical Implications

- Among sesame-sensitized children, a few reacted to oral food challenge for sesame, and Ses i 1-specific IgE level, but not skin prick test, seemed to efficiently predict oral food challenge results.

TO THE EDITOR:

The prevalence of sesame (*Sesamum indicum*) sensitivity in infants confirmed by skin prick test (SPT) was reported to be 2.5%, and the prevalence of challenge-proven sesame allergy was 0.8%¹ in an Austrian population-based study. Ses i 1 (2S albumin) is a novel candidate for use in the diagnosis of sesame allergy, because it is a more indicative sesame allergen component than is sesame serum-specific IgE (sIgE).² SPT has also been used to diagnose sesame allergy.³ However, no data exist on the

comparative diagnostic capacities of sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE, and SPT. Here, we investigated the outcome of oral food challenge (OFC) for sesame as well as the clinical efficacy of Ses i 1-sIgE for predicting OFC results.

We retrospectively analyzed data from children who received OFC with sesame at Sagamiara National Hospital between January 2008 and November 2016 (see this article's Methods section in the Online Repository at www.jaci-inpractice.org). This study included 90 patients aged 1.1 to 14.5 years (median age, 5.5 years) with suspected or definitive sesame allergies (see Figure E1 and Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Eighteen patients (20%) reacted with objective symptoms. Skin symptoms were most common (15 [83%]), followed by gastrointestinal (10 [56%]) and respiratory (9 [50%]) symptoms (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). We observed anaphylactic reactions in 6 patients (33%; see Table E4 in this article's Online Repository at www.jaci-inpractice.org). No patient showed severe symptoms. Fifteen patients (83%) received treatment (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Among the 6 patients who showed anaphylaxis, none required adrenaline injection due to rapid improvement in respiratory symptoms after β_2 -stimulant inhalation.

There was no difference in patient background between challenge-positive and challenge-negative patients (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Among the 26 patients with a history of immediate reaction to sesame, 6 (23%) reacted during OFC. History of immediate

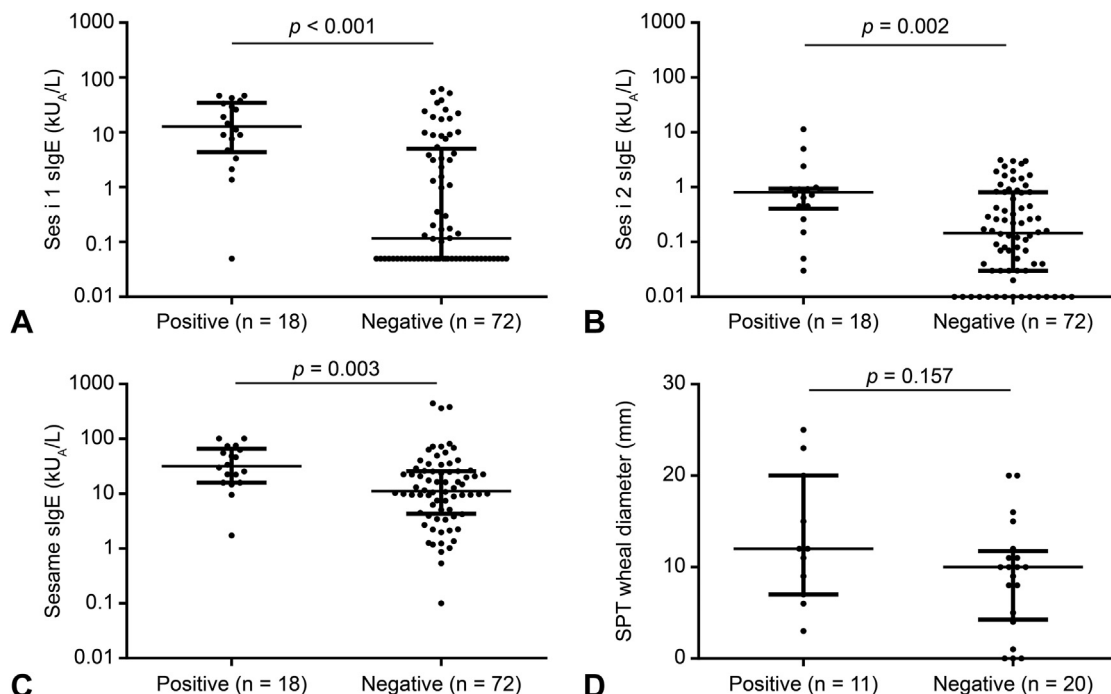


FIGURE 1. Differences in laboratory data between challenge-positive and challenge-negative patients. Dots represent Ses i 1-specific IgE value (A), Ses i 2-specific IgE value (B), sesame-sIgE value (C), and SPT wheal diameter (D).

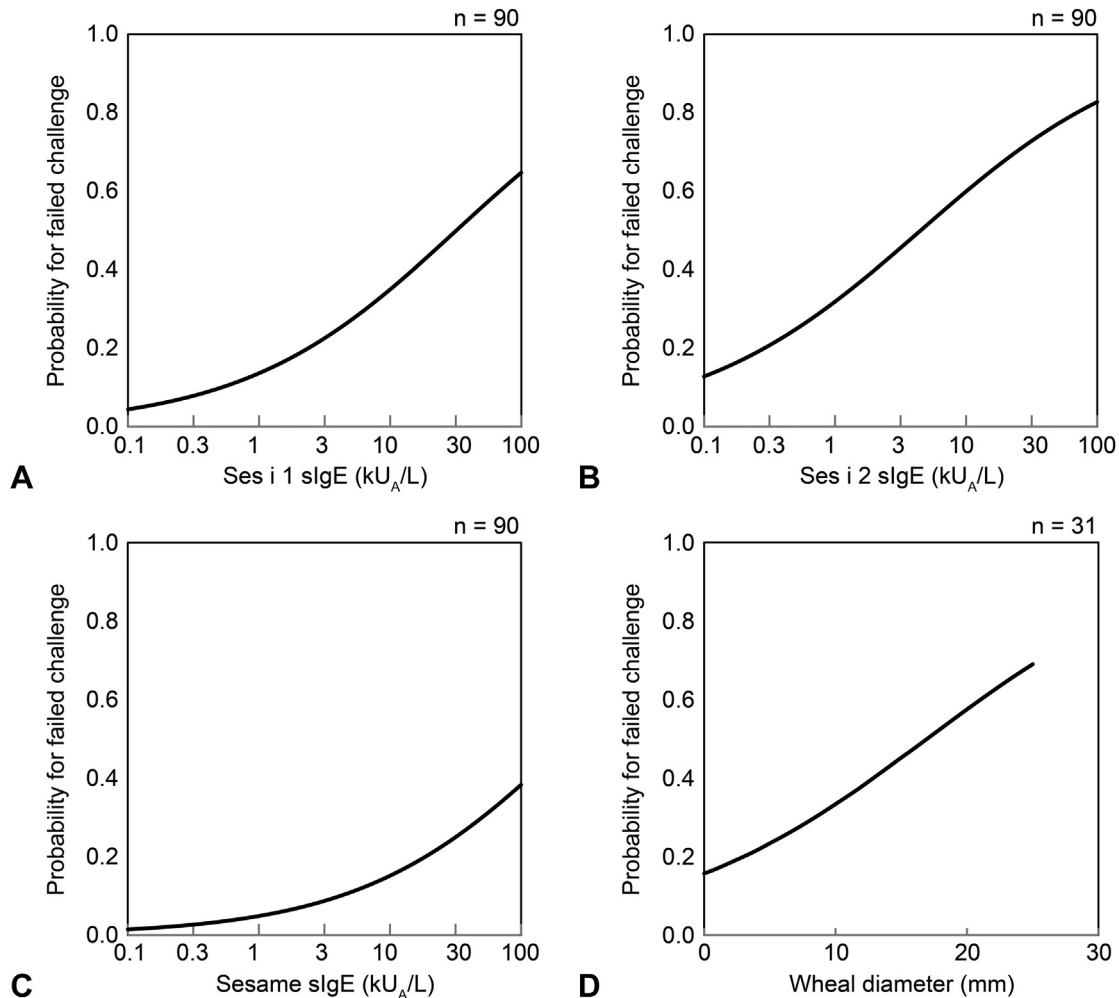


FIGURE 2. Fitted predicted probability curves representing positive OFC outcomes at a given Ses i 1-sIgE value (A), Ses i 2-sIgE value (B), sesame-sIgE value (C), and SPT wheal diameter (D). The solid line represents the probability of any objective reaction.

reaction to sesame did not significantly affect the result of OFC. Patients with positive OFC results had higher sesame-sIgE (31.8 and 11.2 kU_A/L; $P = .003$), Ses i 1-sIgE (12.8 and 0.1 kU_A/L; $P < .001$), and Ses i 2-sIgE (0.8 and 0.1 kU_A/L; $P = .002$) levels. However, there was no significant difference in SPT wheal diameter (12 and 10 mm; $P = .157$) (Figure 1).

The diagnostic capacities of Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter were compared by calculating their respective areas under the receiver operating characteristic curve. The area under the curves (95% CI) for sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter were 0.78 (0.61-0.94), 0.82 (0.66-0.98), 0.78 (0.61-0.94), and 0.66 (0.45-0.87), respectively (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Figure 2 presents fitted predicted probability curves for positive challenge at a given sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE concentration, and SPT wheal diameter. Patient age did not affect the curve (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). We suggest that threshold Ses i 1-sIgE concentrations of 0.13, 0.52, and 32.0 kU_A/L would have an approximately 5%, 10%, and 50% probability, respectively,

of inducing any symptom to sesame (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). We were unable to calculate the serum IgE concentration at which approximately 95% of the patients are predicted to have positive OFC because the possibility of positive OFC in even 100 kU_A/L is less than 95%.

This study revealed that most patients who were sensitized with sesame could safely consume it. This study was also the first to compare diagnostic capacities of sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter.

In our receiver operating characteristic curve analysis, Ses i 1-sIgE is the most indicative parameter for predicting positive OFC. Although Ses i 1-sIgE is effective,² we were unable to calculate a 95% predictive decision point. Nevertheless, at-home consumption of sesame by patients may be permitted if Ses i 1-sIgE level is below 0.13 kU_A/L (5% predicted probability).

Although only 20% of patients with sesame allergy were reported to develop tolerance,⁴ the rate of challenge-confirmed sesame allergy was only one-fifth in the present study, and most patients with a history of immediate reaction to sesame could consume it. In contrast to previous small-scale studies,⁴⁻⁶

we observed no severe symptoms, though half the OFC-positive patients experienced respiratory symptoms. Nevertheless, these respiratory symptoms improved immediately after β_2 -stimulant inhalation. In contrast to current guidelines,⁷ adrenaline was not used in cases presenting with anaphylaxis in our study. Hence, it is crucial to develop education programs for caregivers to increase prompt use of adrenaline.

Sesame may induce severe allergic reactions⁶; therefore, knowing the probability of reaction may help to assess the risk of positive OFC before OFC. Ses i 1-sIgE was more effective than sesame-sIgE in predicting the result of OFC for sesame. Furthermore, Ses i 1-sIgE was more indicative than SPT, which is reported to be slightly more indicative than sIgE.^{3,4} In contrast to previous studies, we found SPT to be ineffective in our study. This indicates that Ses i 1-sIgE may be best suited to contribute to risk assessment before considering OFC for sesame.

There were some limitations to our study. First, we performed SPT on only 31 patients and used a commercially available product in Japan. Not all sesame allergens responsible for clinical symptoms were included in SPT.⁸ It may be better to confirm our results with another commercial sesame extract or component in another study with a larger sample size. Second, Ses i 1-sIgE is currently not commercially available, and current clinical use of Ses i 1-sIgE is limited. Third, the main laboratory tests assessed in this study (sIgE and SPT) were not conducted at the same time, creating a potential bias and possibly rendering any comparison invalid. Finally, potential selection bias may exist in our study. For example, we excluded patients with missing Ses i 1-sIgE data and included only 90 patients. This was done primarily because most patients had an insufficient residual serum sample. In addition, the excluded patients were younger. Therefore, additional, larger prospective studies are needed.

In conclusion, among sesame-sensitized children, OFC-confirmed sesame allergy is uncommon. Therefore, we should increasingly consider OFC for children with sesame sensitization. Ses i 1-sIgE level seemed to be more effective than SPT for diagnosis of sesame allergy. This will facilitate informed decisions for administration of sesame OFC.

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Conflicts of interest: M. Ebisawa is on the DBV Technologies Scientific Advisory Board. The rest of the authors declare that they have no relevant conflicts of interest.

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METHODS

Inclusion criteria

We retrospectively analyzed data from children who received OFC with sesame at Sagamihara National Hospital between January 2008 and November 2016. About 60% of patients were referred from primary care clinics, whereas the remainder were admitted directly without referral. Patients with sesame allergy with a history of immediate reaction to sesame or patients suspected to have sesame sensitivity were enrolled. We included children who first underwent sesame OFC. We excluded children who had missing clinical or laboratory data.

Oral food challenge

Steamed cakes were prepared by mixing 3 g ground white sesame (609 mg sesame protein) with pumpkin and sugar and heating in a 1000-W microwave oven for 90 seconds, according to the 2017 Japanese pediatric guidelines for food allergy.^{E1} Initially, 0.1 to 0.2 g ground sesame seeds were administered to patients every 15 to 30 minutes, which was increased to a cumulative dose of at least 3 g. Definition of anaphylaxis and treatments for provoked reaction were based on the European Academy of Allergy and Clinical Immunology's food allergy and anaphylaxis guidelines,^{E2} and severity of symptoms was defined according to the 2017 Japanese pediatric guidelines for food allergy.^{E1}

Laboratory data

We measured sesame-sIgE, Ses i 1-sIgE, and Ses i 2-sIgE within 180 days (median, 105 days; range, 4-180 days) of OFC using the ImmunoCAP assay system (Thermo Fisher Scientific/Phadia, Uppsala, Sweden). Ses i 1-sIgE and Ses i 2-sIgE were analyzed using stored serum samples at Kyoto University according to previously described methods.^{E3} The serum samples were stored at -80°C for a median of 4.2 years before analysis (range, 1.6-11.8 years).

Skin prick test

We performed the SPT using a sterile bifurcated needle (Precision Medical Products, Denver, Pa) and commercial sesame extract (1:10 ratio; Torii Pharmaceutical, Tokyo, Japan).^{E4}

An allergist performed the SPT during patient hospitalization for OFC. In the SPT, we evaluated maximum wheal size 15 minutes after skin prick, as previously described.^{E4} We defined sensitization as a wheal size of 3 mm or greater.

Diagnostic performance capacity of Ses i 1-sIgE and other variables

The diagnostic capacities of Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter were compared by calculating their respective areas under the receiver operating characteristic curve. Receiver operating characteristic curve analyses for sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter for positive OFC were performed for patients with SPT data. The area under the curves (95% CI) for sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter were analyzed.

Statistical analysis

Data were expressed as median values and interquartile ranges, and the Mann-Whitney *U* or Fisher exact test was used for statistical comparison as appropriate. *P* values of less than .05 were considered statistically significant. Univariable and multivariable analyses using logistic regression were performed. Probability curves were created using regression analysis after logarithmic transformation of sIgE values. Ses i 1-sIgE was converted to 0.005 kU_A/L if less than 0.01 kU_A/L. Ses i 2-sIgE was converted to 0.0005 kU_A/L if less than 0.001 kU_A/L. Area under the receiver operating characteristic curve and 95% CI for positive OFC results for sesame-sIgE, Ses i 1-sIgE, and Ses i 2-sIgE levels, and SPT wheal diameter were calculated. We used SPSS 24.0 (IBM Corporation, Armonk, NY) to perform all statistical analyses.

Ethical considerations

In accordance with the Declaration of Helsinki, the study design and risks of anaphylaxis during OFC were fully explained both orally and in writing to patients and their guardians, and we obtained written informed consent from all participants for OFC and publication of the data. Before analysis, all patient data were anonymized. Approval was obtained from the institutional review board of Sagamihara National Hospital in 2014 (approval no. 2014-1-5).

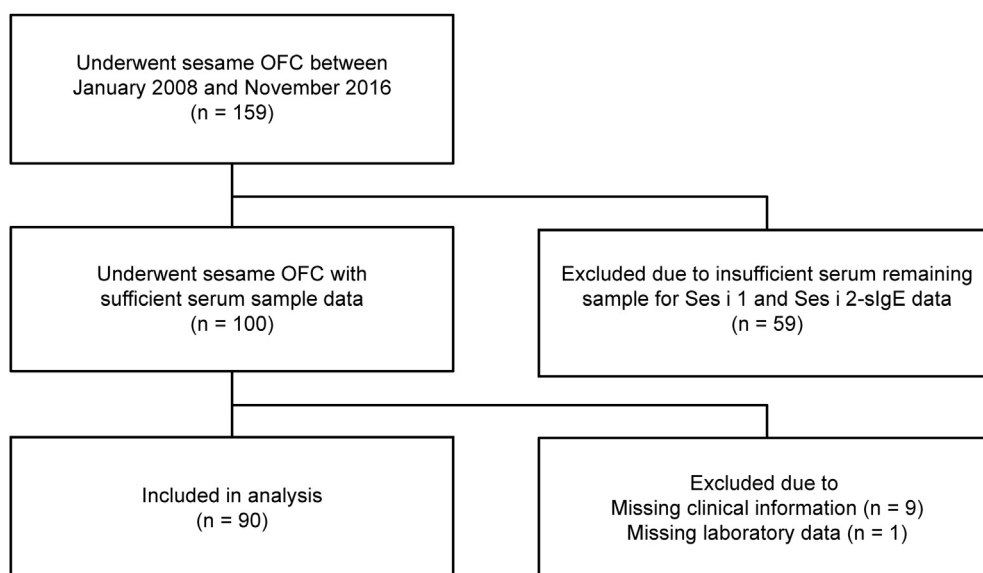


FIGURE E1. Study participation. The 90 included patients with suspected or definitive sesame allergies were aged 1.1 to 14.5 years (median, 5.5 years). Twenty-six had histories of reaction to sesame, and none had history of anaphylaxis due to sesame. All suspected patients with sesame allergy had other food allergies. Median sesame-sIgE, Ses i 1-sIgE, and Ses i 2-sIgE levels were 16.1, 0.7, and 0.2 kU_A/L, respectively.

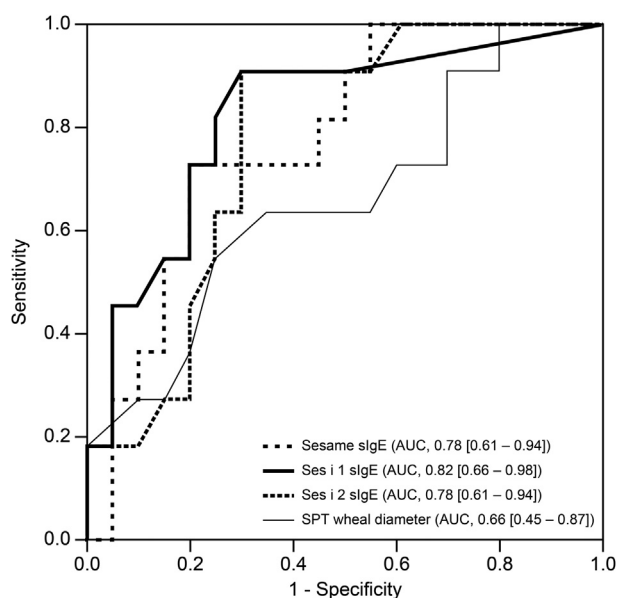


FIGURE E2. ROC analyses to diagnose sesame allergy by OFC. AUCs (95% CI) for sesame-sIgE, Ses i 1-sIgE, Ses i 2-sIgE, and SPT wheal diameter were done ($n = 31$). In ROC analyses of sesame-sIgE, Ses i 1-sIgE, and Ses i 2-sIgE in all patients ($n = 90$), AUCs were 0.73 (0.60-0.85), 0.81 (0.71-0.91), and 0.73 (0.62-0.85), respectively. *AUC*, Area under the curve; *ROC*, receiver operating characteristic.

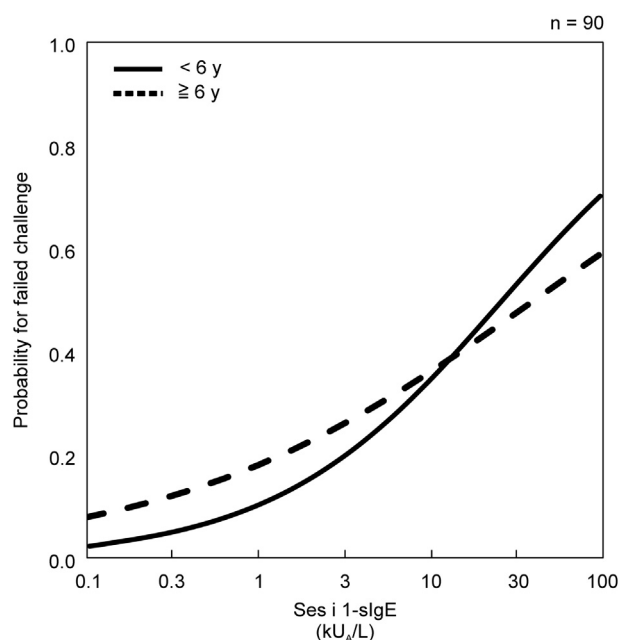


FIGURE E3. Fitted probability curve representing positive OFC outcomes at a given Ses i 1-IgE value. The probability curve was subdivided by patients 6 years or younger. The solid line represents the probability of any objective reaction for patients younger than 6 years.

TABLE E1. The patients' clinical and demographic characteristics

Characteristic	Included patients (n = 90)	Excluded patients (n = 59)	P value
Sex (male)	54 (60%)	39 (66%)	.492
Age (y)	5.5 (2.8-7.3)	4.0 (2.5-6.1)	.026
History of immediate reaction to sesame	26 (29%)	22 (37%)	.289
History of anaphylaxis to sesame	0 (0%)	3 (5%)	.060
Atopic dermatitis, current	47 (52%)	18 (31%)	.011
Bronchial asthma, current	14 (16%)	6 (10%)	.463
Allergic rhinitis, current	10 (11%)	4 (7%)	.567
Total IgE (IU/mL)	981 (355-2030)	816 (166-2110)	.620
Sesame-sIgE (kU _A /L)	16.1 (6.0-34.1)	15.5 (3.2-32.7)	.383

Values are expressed as n (%) or median (interquartile range).

P values represent statistical significance between nonanaphylactic cases and anaphylactic cases.

TABLE E2. The patients' clinical and demographic characteristics

Characteristic	Reactive (n = 18)	Asymptomatic (n = 72)	P value
Sex (male)	9 (50%)	45 (63%)	.422
Age (y)	6.1 (5.0-7.1)	5.3 (2.5-7.6)	.195
History of immediate reaction to sesame	6 (33%)	20 (28%)	.772
History of anaphylaxis to sesame	0 (0%)	0 (0%)	>.999
Peanut allergy	11 (61%)	28 (39%)	.113
Atopic dermatitis, current	9 (50%)	38 (53%)	>.999
Bronchial asthma, current	3 (17%)	11 (15%)	>.999
Allergic rhinitis, current	3 (17%)	7 (10%)	.412
Total IgE (IU/mL)	1106 (556-1993)	981 (303-2930)	.329

Values are expressed as n (%) or median (interquartile range).

TABLE E3. Data related to induced reactions and positive challenge severity

Symptoms	Positive sesame OFC (n = 18)
Skin	15 (83%) Pruritus (n = 10), wheal (n = 7), urticaria (n = 6), exanthema (n = 6)
Gastrointestinal	10 (56%) Abdominal pain (n = 5), emesis (n = 5), pruritus of the throat (n = 2), diarrhea (n = 1)
Respiratory	9 (50%) Cough (n = 8), wheeze (n = 4), chest tightness (n = 1)
Neurological	3 (17%) Change in activity level (n = 3)
Cardiovascular	0 (0%)
Anaphylaxis	6 (33%)
Severity	
Mild	2 (11%)
Moderate	16 (89%)
Severe	0 (0%)

Data are expressed as n (%).

Some symptoms overlap with other symptoms.

Severity was defined according to the 2017 Japanese Pediatric Guideline for Food Allergy.

TABLE E4. Details of patients who showed anaphylaxis during OFC

		Symptom					Treatment				
Age (y)	Sex	Skin	Gastrointestinal	Respiratory	Neurological	Antihistamine	β 2-stimulant inhalation	Steroid	Drip infusion	Reason not to use adrenaline	
3	M	Wheal, pruritus	Emesis	Cough, wheeze	—	+	+	—	—	Improvement immediately after β 2-stimulant inhalation	
4	M	Urticaria, pruritus	Abdominal pain	Cough	Change in activity level	+	+	—	—	Improvement immediately after β 2-stimulant inhalation	
5	M	Urticaria, wheal, pruritus	—	Cough	—	+	+	—	—	Improvement immediately after β 2-stimulant inhalation	
5	F	Wheal, pruritus	—	Cough, wheeze	—	+	+	—	—	Improvement immediately after β 2-stimulant inhalation	
5	F	Wheal, pruritus	—	Cough, wheeze	—	—	+	—	—	Improvement immediately after β 2-stimulant inhalation	
12	M	Urticaria	Abdominal pain	Chest tightness	—	+	+	+	+	Improvement immediately after β 2-stimulant inhalation	

F, Female; M, male.

F, Female; M, male.

TABLE E5. Treatments for patients with positive challenge results

Treatment	Positive sesame OFC (n = 18)
Antihistamine	12 (67%)
β 2-stimulant inhalation	8 (44%)
Steroid	3 (17%)
Drip infusion (intravenous)	1 (6%)
Adrenaline (intramuscular)	0 (0%)
No treatment	3 (17%)

Data are expressed as n (%).

Some treatments overlap with other treatments.

TABLE E6. Predictive probability of sesame-sIgE, Ses i 1-sIgE, and Ses i 2-sIgE for positive OFC for sesame

	Predicted probability				
	5%	10%	50%	90%	95%
Sesame-sIgE (kU _A /L)	1.06	4.2	NE	NE	NE
Ses i 1-sIgE (kU _A /L)	0.13	0.52	32.0	NE	NE
Ses i 2-sIgE (kU _A /L)	NE	0.06	4.5	NE	NE

NE, Not estimated.

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